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Survey

Neuroendocrine cells derived chemokine vasoactive intestinal polypeptide (VIP) in allergic diseases

Alok K. Verma, Murli Manohar, Sathisha Upparahalli Venkateshaiah, Anil Mishra*

Department of Medicine, Section of Pulmonary Diseases, Tulane Eosinophilic Disorders Center, Tulane University School of Medicine, New Orleans, LA 70112, USA

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ABSTRACT

Worldwide increase incidences of allergic diseases have heightened the interest of clinicians and researchers to understand the role of neuroendocrine cells in the recruitment and activation of inflammatory cells. Several pieces of evidence revealed the association of neuropeptides in the pathogenesis of allergic diseases. Importantly, one such peptide that is secreted by neuronal cells and immune cells exerts a wide spectrum of immunological functions as cytokine/chemokine is termed as Vasoactive Intestinal Peptide (VIP). VIP mediates immunological function through interaction with specific receptors namely VPAC-1, VPAC-2, CRTH2 and PAC1 that are expressed on several immune cells such as eosinophils, mast cells, neutrophils, and lymphocytes; therefore, provide the basis for the action of VIP on the immune system. Additionally, VIP mediated action varies according to target organ depending upon the presence of specific VIP associated receptor, involved immune cells and the microenvironment of the organ. Herein, we present an integrative review of the current understanding on the role of VIP and associated receptors in allergic diseases, the presence of VIP receptors on various immune cells with particular emphasis on the role of VIP in the pathogenesis of allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. Being crucial signal molecule of the neuroendocrine-immune network, the development of stable VIP analogue and/or antagonist may provide the future therapeutic drug alternative for the better treatment of these allergic diseases. Taken together, our current review summarizes the current understandings of VIP biology and further explore the significance of neuroendocrine cells derived VIP in the recruitment of inflammatory cells in allergic diseases that may be helpful to the investigators for planning the experiments and accordingly predicting new therapeutic strategies for combating allergic diseases. Summarized graphical abstract will help the readers to understand the significance of VIP in allergic diseases.

1. Introduction

In the last few decades, the allergic diseases have become more prevalent affecting up to 20–30% of the world population that results in lower life quality [1,2]. The condition becomes worse as the occurrence of one allergic disease leads to predisposition for another [3]. Importantly, the recent advances to understand the pathogenesis of allergic diseases have highlighted the neuroimmune interaction as a crucial player in the development of allergic diseases; therefore, the understanding of neuroimmune communication is particularly required for gaining the better knowledge in the context of allergic diseases [4]. The link between the neuroendocrine system and the immune system depends upon the several key factors such as the secretion of neuropeptides by immune cells and cytokines by neuroendocrine cells, the presence of shared receptors on the cells for both the systems, the effect of neuropeptides and cytokines on immunological and neurological functions respectively. All these regulatory processes provide the basis for neuropeptides to function as cytokine or chemokine in the immune system thereby modulating the provoked immune responses [5]. Interestingly, the large number of neuropeptides such as Calcitonin Gene-Related Peptide (CGRP), Substance P (SP), Protein gene product 9.5, Neuropeptide Y, Nerve growth factor, and Vasoactive Intestinal Peptide (VIP) have been implicated in the pathogenesis of the allergic diseases [6,7]. However, in the last decade, VIP has emerged as one such potent neuropeptide that exerts a wide spectrum of immunological functions controlling both innate and adaptive immunity. VIP exerts its

Abbreviations: VIP, Vasoactive Intestinal Peptide; VPAC-1, Vasoactive Intestinal Peptide Receptor Type 1; VPAC-2, Vasoactive Intestinal Peptide Receptor Type 2; CRTH2, Chemoattractant Receptor-Homologous Molecule Expressed on Th2 Cells; PAC1, Pituitary adenylate cyclase-activating polypeptide (PACAP) receptor; GPCR, G protein-coupled receptor; PGs, Prostaglandins; DC, Dendritic cell; MCP-1, Monocyte chemotactic protein 1; CNS, Central nervous system; PGD2, Prostaglandin D2; AR, Allergic rhinitis; AD, Atopic dermatitis; CGRP, Calcitonin Gene-Related Peptide; SP, Substance P; ELISA, Enzyme-linked immunosorbent assay; IL, Interleukin; Mw, Molecular weight; EoE, Eosinophilic esophagitis

* Corresponding author.
E-mail address: amishra@tulane.edu (A. Mishra).

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Table 1
Characterization of VIP associated receptors.

Receptors	VPAC-1	VPAC-2	PAC1	CRTH2
Gene name	*VIPR1*	*VIPR2*	*ADCYAP1R1*	*PTGDR2*
Human chromosome location	3p22	7q36.3	7p14	11q12.2
Receptor type	G-protein coupled receptor	G-protein coupled receptor	G-protein coupled receptor	G-protein coupled receptor
Tissue expression	CNS and peripheral tissues including liver, lung and intestine	CNS and Peripheral tissues, including smooth muscles in cardiovascular, gastrointestinal and reproductive systems	CNS, anterior pituitary, pancreatic acini, uterus, and adrenal medulla	CNS, thymus, digestive tract, heart, spleen, spinal cord, skeletal muscle
mRNA expression on immune cells	T lymphocytes, Neutrophils, Monocytes, Macrophages, Thymocyte, Keratinocyte THP-1 (monocytic)	Mast cells, Thymocyte, Keratinocyte. Lymphocytes, Macrophages (Upon activation)	Macrophages THP-1 (monocytic)	Eosinophils, Basophils, Th2 cells, Mast cells, monocytes
Selective agonists	[Ala^{11,22,28}]VIP [K15, R16, L27]VIP(1–7)/ GRF(8–27)-NH2	Ro 25–1392; Ro 25–1553	Maxadilan	Delta12-prostaglandin D2; Δ12-Prostaglandin D2; L-888,607
Selective antagonist	PG97-269	PG99-465	Max.d.4; M65; PACAP (6–38).	Ramatroban; OC000459 Fevipiprant; Setipiprant.
VIP mediated Signaling mechanism	Primarily coupled to adenylate cyclase	Primarily coupled to adenylate cyclase	Adenylate cyclase/protein kinase A (PKA) and phospholipase C (PLC)/ protein kinase C (PKC) pathways	VIP-CRTH2 ligation involved Ca2+ independent PKC and PKA cytosol-to-membrane translocation

biological function by regulating the production of both anti- and pro-inflammatory mediators. In terms of innate immunity, VIP inhibits the production of inflammatory cytokines and chemokines from immune cells as well as reduces the expression of co-stimulatory molecules on antigen-presenting cells that reduces the stimulation of antigen-specific CD4 + T cells. Additionally, in adaptive immunity, VIP promotes T-helper (Th)2 type immune responses and reduces inflammatory Th1 type responses [8].

VIP is 28-amino acid peptide hormone that was originally isolated as a vasodilator peptide from the intestine [9,10]. VIP is reported as one of the most abundant neuropeptides of the human body and secreted in the significant amount in the central and peripheral nervous systems as well as in various peripheral tissues and organs [11]. Although VIP is primarily secreted by neuronal tissue, it is also produced by several immune cells such as eosinophils, mast cells and lymphocytes [12–14]. The secreted VIP like cytokine or chemokine has the ability to regulate the homeostasis of the immune system. The expression of VIP is noticed in the brain, heart, lungs, kidney, urinary bladder, pancreas and gastrointestinal tract [15]. Importantly, the sequence of VIP peptide is well conserved among the different species and is identical in human, mice, cow, pig and dog species suggesting the significance of this neuropeptide in immunomodulation [16]. Further, the presence of VIP-containing nerves near the elements of the immune system and the presence of VIP receptors on immune cells indicate the interaction of VIP with immune system [11]. The immunological responses of VIP are mediated through interaction with specific receptors namely Vasoactive Intestinal Peptide Receptor Type 1 (VPAC-1), Vasoactive Intestinal Peptide Receptor Type 2 (VPAC-2), Chemoattractant Receptor-Homologous Molecule Expressed on Th2Cells (CRTH2) and Pituitary adenylate cyclase-activating polypeptide (PACAP) receptors (PAC1) that are present on different types of immune cells [17,18]. In addition, the emerging pieces of evidence have indicated that VIP and its receptors mediated signaling plays the decisive role in the pathogenesis of allergic diseases such as asthma, allergic rhinitis, dermatitis and food allergy [18–20]. Therefore, it will be of great significance to explore the mechanistic pathways involved in VIP mediated biological effect on the immune system that may open the novel avenues for therapeutic intervention in allergic diseases. The review provides most current knowledge and understanding of VIP mediated diverse biological functions on the immune system, the interaction of VIP with specific receptors that are expressed on various immune cells, further to understand the VIP induced signaling pathways with special attention on the impact of VIP in the pathogenesis of allergic diseases. Furthermore, exploring the pathways involved in cross-talk between the nervous and immune system may be useful for understanding the neuropeptide mediated signaling events in the pathophysiology of allergic diseases. The summarized information will be helpful to propose VIP and its agonists/antagonists as promising alternative candidates for the treatment of the allergic diseases.

2. General characteristics of vasoactive intestinal peptide and its receptors

VIP was first isolated from swine duodenum and named so because of its vasodilating action that modifies the intestinal blood flow [10]. VIP works as 'cytokine-like peptide' and exerts a wide spectrum of biological functions through specific receptors present on immune effector cells, thus triggering a signal transduction cascade, and regulating the immunological response by the production of both anti and pro-inflammatory mediators [21,22]. Basically, human VIP gene encodes 7 exons and is localized to chromosome 6q25.2. VIP is synthesized as a precursor molecule where VIP is encoded by the fifth exon and signal peptide of 22 amino acids by the second exon. The active VIP molecule of 28 amino acids is produced after the processing of precursor molecule [23,24]. VIP is reported to have the helical conformation with one α-helix (residues 11–26) and two β-bends (residues 2–5 and 7–10) at the N-terminus [25]. As VIP has high similarity in primary and secondary structures with glucagon/secretin, thus VIP classified with these peptides in glucagon/secretin superfamily, the ligand of class II G protein–coupled receptors. This family also includes peptides such as glucagon-like peptides (GLPs), gastric inhibitory polypeptide (GIP), corticotropin-releasing factor (CRF), growth hormone-releasing factor (GRF), parathyroid hormone (PTH), calcitonin and pituitary adenylate cyclase-activating peptide (PACAP) [26]. VIP expressed in numerous organs, and tissues at various concentrations thereby exert an array of different biological effects in the body. The biological functions of VIP are mediated via specific receptors namely VPAC-1, VPAC-2, CRTH2 and PAC1 that are expressed on immune cells. VIP having low affinity for PAC1 while for remaining receptors affinity is comparatively high. The general characteristics of VIP receptors are

summarized in Table 1.

2.1. VPAC receptors (VPAC-1 & VPAC-2)

The VPAC receptors (VPAC-1 & VPAC-2) are widely distributed in the body suggesting the crucial role in the diverse immunological processes [27]. These VPAC receptors belong to the subfamily of G protein-coupled receptor family (GPCR) known as class B GPCR. This subfamily is also known as 'secretin-like' receptors family because the secretin receptor was the first member of a new GPCR family. These receptors consist of one polypeptide chain with seven transmembrane segments having N-terminal extracellular domain and C-terminal cytoplasmic end [28]. VPAC-1 receptors are mainly expressed in the central nervous system (CNS), liver, lung, breast, kidney, prostate, spleen, mucosa of stomach and small intestine [29] while VPAC-2 receptors have been localized in the CNS, pancreas, lung, heart, kidney, stomach skeletal muscle, smooth muscle, adipose tissue, and thyroid follicular cells [30]. Structurally, VPAC-1 receptor consists of 457 amino acids with a long extracellular N-terminal having Mw of 52 kDa. VPAC-1 receptor gene (*VIPR1*) is composed of 13 exons ranging in size from 42 to 1400 bp and located on short arm of human chromosome 3 (3p22) [31,32]. However, VPAC-2 receptor consists of 438 amino acids with Mw of 49 kDa. The human VPAC-2 receptor gene (*VIPR2*) is reported to be present on chromosome 7q36.3 and encoded by 13 exons [33,34]. Both VPAC-1 and VPAC-2 receptors possess highly conserved amino acid sequence suggesting that these receptors may be evolved from a common ancestral gene thereby transduce the signal in the same way from the extracellular surface to the underlying involved molecules upon ligand binding [35]. Importantly, VPAC-1 receptors are expressed constitutively on T cells, monocytes, and macrophages whereas the expression of VPAC-2 receptors are induced on T cells and macrophages only after bacterial/or viral infections [36].

These VPAC receptors also interact with few accessory proteins that modulate the signaling events. These proteins are commonly known as accessory proteins' or 'GPCR interacting proteins which provided a new concept in GPCR signaling to transduce the signals independently of the G-proteins [37]. GPCR mediated signaling is also affected by Calmodulin (CaM) i.e. a calcium-binding messenger protein expressed in all eukaryotic cells. Upon binding to Ca^{2+}, Calmodulin acts as part of calcium signal transduction pathway by promoting the different modes of association with many target protein such as kinases or phosphatases as well as GPCR signaling involved enzymes such as adenylyl cyclase, phospholipases etc [38]. Another study by Gee et al. (2009) suggested that S-SCAM (synaptic scaffolding molecule), also named membrane-associated guanylate kinase inverted-2 (MAGI-2), interacts and regulates VPAC-1 receptor intracellular localization in epithelial cells and also inhibits VPAC-1 agonist-induced activation and internalization. The physical interaction between VPAC-1 receptor and S-SCAM was confirmed by immunoprecipitation in HEK 293 mammalian cells and human pancreatic and colonic tissues [39].

2.2. Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) receptor

In the recent years, the involvement of CRTH2 receptor in the allergic diseases has gained much attention due to its presence on the inflammatory cells such as eosinophils, basophils, and Th2 lymphocytes [40,41]. CRTH2 receptor is G protein-coupled receptor (GPCR) containing seven putative transmembrane domains. CRTH2 also designated as Prostaglandin D_2 receptor 2 (DP_2), and cluster of differentiation 294 (CD294) is encoded by the *PTGDR2* gene in human. Several pieces of evidence indicate that CRTH2 receptor may play an important role in the allergic diseases, since the blockade of this receptor reduces the allergic airway inflammation [42,43]. Further, the previous findings have highlighted the role of Prostaglandin D2 (PGD2) and CRTH2 receptor interaction in the pathogenesis of allergic diseases [44]. Generally, PGD2 is a major arachidonic acid metabolite released from immune cells such as mast cell [45], and Th2 cells [46]. In addition, several other studies implicate PGD2-induced inflammatory cells recruitment in allergic diseases that are mediated via CRTH2 receptor [40,47] and blockage of this novel CRTH2 receptor attenuates the allergic manifestation in the patients [48,49]. However, recently, the novel association between VIP and CRTH2 receptor in recruiting eosinophils in allergic rhinitis patients have been reported. Interestingly, the activation of CRTH2 receptor expressed on human eosinophils by VIP was noticed and further, the ability of VIP to induce protein synthesis of CRTH2 and its surface expression was reported [18]. This study points the possible role of VIP and CRTH2 receptor interaction in modulating the other allergic diseases and there is still need more efforts in this direction.

2.3. Pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1)

VIP also interacts with another member of GPCRs known as Pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1). PAC1 receptor was first identified in a rat pancreatic acinar carcinoma cell line [50]. With respect to the tissue, the expression of PAC1 receptor is particularly observed in CNS, the anterior pituitary, pancreatic acini, uterus, and predominantly in the adrenal medulla [51]. Notably, VPAC receptors respond to both VIP and PACAP with high affinity whereas PACAP has more than > 100-fold affinity as compared to VIP for PAC1 receptor suggesting the minimal role of this receptor in VIP mediated allergic diseases [52]. However, the study performed by Lauenstein et al. (2011) suggested that PAC1 receptor mediates anti-inflammatory effects in allergic airway inflammation. Thus, PAC1 receptor agonists may be a promising candidate in airway allergic diseases such as bronchial asthma [53].

3. Vasoactive Intestinal Peptide receptors expression on the immune cells

The significance of VIP in the immune system is further enhanced due to its ability to interact with multiple immune cells such as mast cells, eosinophils, neutrophils, lymphocytes, dendritic cells, NK cells, and macrophages through VIP associated receptors VPAC-1, VPAC-2, PAC1 and CRTH2 [36,54].

3.1. Mast cells, basophils, and VIP receptors expression

Mast cells have an important regulatory role in innate as well as adaptive immunity and act as effector cells that manifest the allergic disorders via releasing allergic mediators such as histamine, leukotrienes, prostaglandins, cytokines, proteases, and heparin. Generally, mast cells perform the biological functions via FcεRI mediated degranulation; however, these mast cells also respond to neuropeptides during inflammation in FcεRI independent manner. Further, FcεRI-independent activation of human mast cells and their presence in the close proximity of neurons suggest the mast cell and neuropeptides interaction in the pathophysiology of allergic diseases [4,55]. The late phase response in asthma is mediated by activation of human mast cells by neuropeptides that may indirectly provoke inflammation via cellular recruitment [56]. Furthermore, human mast cells degranulation and production of chemokines mainly MCP-1, inducible protein-10, RANTES and IL-8 occurs in response to neuropeptides including VIP. These secreted chemokines, in turn, recruit the other immune cells such as eosinophils, monocytes, and neutrophils [57]. Moreover, Groneberg et al. (2003) reported VPAC-2 mRNA expression in human skin mast cells, as well as human mast cell line (HMC-1) and down-regulation of this VPAC-2 receptor in human mast cells in acute lesions of atopic dermatitis was noticed highlighting the significance of VPAC-2 receptor and mast cell interaction in allergic disease pathophysiology [58].

Consistent with the earlier study, VIP mediated activation and degranulation of both human cultured mast cells LAD2 and primary cultured human mast cells were observed. In addition, real-time PCR analysis showed that LAD2 express mRNA for VPAC-2 but not VPAC-1 receptor. The expression of VIP and its receptors is enhanced particularly in mast cell-mediated inflammatory diseases suggesting that VIP may cause *in vivo* mast cell activation [57]. The tryptase serum levels were also correlated significantly with neuropeptide levels demonstrating the involvement of neuropeptides in the pathomechanism of mastocytosis [59]. In addition, VIP also governs intestinal barrier function and inflammation as stresses disturb follicle-associated epithelium by VIP and VPAC receptors mediated mechanism on mucosal mast cells [60]. Furthermore, when murine mast cells were cultured in the presence of IgE that subsequently lead to stimulation and release of truncated VIP together with histamine [13]. Importantly, the expression of CRTH2 receptor was also reported on mast cells and basophils. In human nasal polyps, 34% of mast cell express CRTH2 receptor. Additionally, 87% of LAD2 human mast cell line and 98% of primary cultured human mast cell showed expression of intracellular CRTH2 [61]. The expression of CRTH2 receptor has also been noticed on basophils that may be responsible for chemotaxis of these cells at the inflammatory site [41,62]. Together, current evidence suggests that the expression of VIP specific receptors on mast cells and basophils provide an opportunity for neuropeptide VIP to act on these cells and modulate the immunological reactions. We recently reported the expression of CRTH2 receptor on tissue mast cells of eosinophilic esophagitis (EoE) patients and its significance in the experimental murine model of EoE [63].

3.2. Eosinophils and VIP receptors expression

Eosinophils are responsible for combating multicellular parasites in vertebrates. Along with mast cells, the molecular and cellular mechanisms related to eosinophils in allergic diseases such as asthma, rhinitis, eosinophilic gastrointestinal disorders, and eosinophilic pancreatitis is well studied [64–68]. Despite considerable advances in understanding eosinophil-mediated allergic manifestations, the impact of neuropeptides on eosinophils in allergic disease is vastly under-studied. Only a few earlier reports have pointed out the immuno-regulatory effect of neuropeptides on eosinophils [69,70]. A recent report showed the role of VIP and CRTH2 receptor interaction in recruiting eosinophils in allergic rhinitis (AR) patients [18]. The relatively high expression of CRTH2 receptor in various regions of the brain was observed indicating the association between neuropeptide and CRTH2 receptor. These evidence point out that VIP/CRTH2 receptor interaction may play a crucial role in allergic manifestations through its stimulatory effects on Th2 cells, eosinophils, and basophils [71]. The secretion of VIP by eosinophils is also reported [12]. All these functional studies have pointed out a strong association between VIP and eosinophils in the pathophysiology of allergic diseases. However, the role of PGD2-CRTH2 interaction in chemotaxis of eosinophils in allergic condition has also been reported [40,47]. Additionally, in nasal tissue of AR patients, ligation of PGD2 to CRTH2 receptor appears to be selectively involved in eosinophils recruitment. However, the amount of CRTH2 but not PGD2 was highly and significantly correlated with the number of eosinophils infiltrating into nasal mucosa suggesting the involvement of another factor in eosinophils trafficking [72]. Recently, the involvement of CRTH2 receptor in modulating the biochemical events in VIP-induced eosinophil chemotaxis in AR patients was reported [18]. Our study also reported CRTH2 receptor expression on blood and tissue eosinophils in EoE patients [63].

The significant decrease in inflammatory biomarkers such as eosinophil peroxidase (EPO), myeloperoxidase and lactate dehydrogenase were observed in the lung of OVA-respirable powder challenged murine model when intra-tracheal administration of IK312532-respirable powder (Long-acting analogue of VIP) was done. These results reveal the VIP mediated attenuation of existing eosinophilia in the lung [73]. Taken together, it seems reasonable that the association exists between eosinophils and VIP in the allergic diseases. This interaction needs further investigation to explore the VIP biology with respect to eosinophils in allergic diseases.

3.3. Neutrophils and VIP receptors expression

O'Dorisio et al (1980) detected VIP in neutrophils isolated from leukaemic patients that may provoke either inhibitory or/excitatory response upon neutrophils and this action is mediated through VPAC-1 receptor. The expression of VPAC-1 receptor on human resting neutrophils was first detected by RT-PCR analysis [74]. Palermo et al. (1996) demonstrated that VIP has the ability to affect the expression of receptors for Fc portion of IgG (Fcγ R) in human neutrophils. In the experiment, antibody dependent cellular cytotoxicity (ADCC) activity was evaluated in basal conditions and following *in vitro* stimulation with interferon gamma (IFNγ). The incubation with VIP reduced the cytotoxicity of both stimulated and non-stimulated neutrophils. The inhibitory effect of VIP was more pronounced on neutrophils stimulated with IFNγ. Thus, by regulating the neutrophil cytotoxic response, VIP may limit tissue injury during inflammation [75]. The priming of neutrophils by VIP has also been reported [76,77]. Additionally, VIP peptide analogue could inhibit antigen-or cytokine-induced neutrophil recruitment *in vivo* in airways [78].

3.4. Lymphocytes and VIP receptors expression

Both T and B lymphocytes express VIP associated receptors [79] and the expression of VPAC-1 receptor on murine CD4+ and CD8+ T-cells point out the effect of VIP on cytokine production and proliferation of T-lymphocytes [80]. However, another study has demonstrated the presence of both VPAC-1 and VPAC-2 receptors on CD4+ and CD8+ T cells [81]. VIP as immunomodulatory neuropeptide has the ability to promote or inhibit individually the differentiation or function of some T-helper subsets [82]. Both T and B lymphocytes produce VIP suggesting the lymphocytes may modulate the immune response through secretion of VIP [14,83,84].

The expression of CRTH2 receptor has also been reported on T lymphocytes and it is preferentially expressed on Th2 cells [85]. The role of CRTH2 receptor in mediating chemotaxis of CD4+ Th2 lymphocytes in response to mast cell released substances has been observed [86]. Further, the migration of Th2 cells through a CRTH2 dependent mechanism via mast cells released mediators in nasal polyp tissue has also been reported [87]. More studies needed in this direction to explore the effect of lymphocyte and VIP interaction on the immune system.

3.5. Monocytes, macrophages, dendritic cells and VIP receptors expression

Monocytes are the part of the innate immune system and also have the prominent effect on adaptive immunity. The inhibitory or stimulatory effect of VIP on monocytes or macrophages depends upon the expression of specific receptors at the differentiated or activated cells that lead to activation of different transduction pathways and subsequently distinct immune response [88]. Importantly, in resting human monocytes, the expression of VPAC-1 was reported but not VPAC-2 receptor [89]. Murine peritoneal macrophages, and the human monocytic cell line THP-1 express VPAC-1 and PAC1 mRNA constitutively, and VPAC-2 following LPS stimulation [90,91]. Interestingly, VIP shows the inhibitory effect on LPS-induced inflammatory responses by murine monocytes and macrophages that is mediated via VPAC-1 receptor, even though both VPAC-1 and VPAC-2 receptors are expressed [92]. Additionally, VIP exerts anti-inflammatory action by inhibition of pro-inflammatory cytokine production (such as TNFα, IL-6, IL-12) by activated macrophages; and by up-regulation of anti-inflammatory

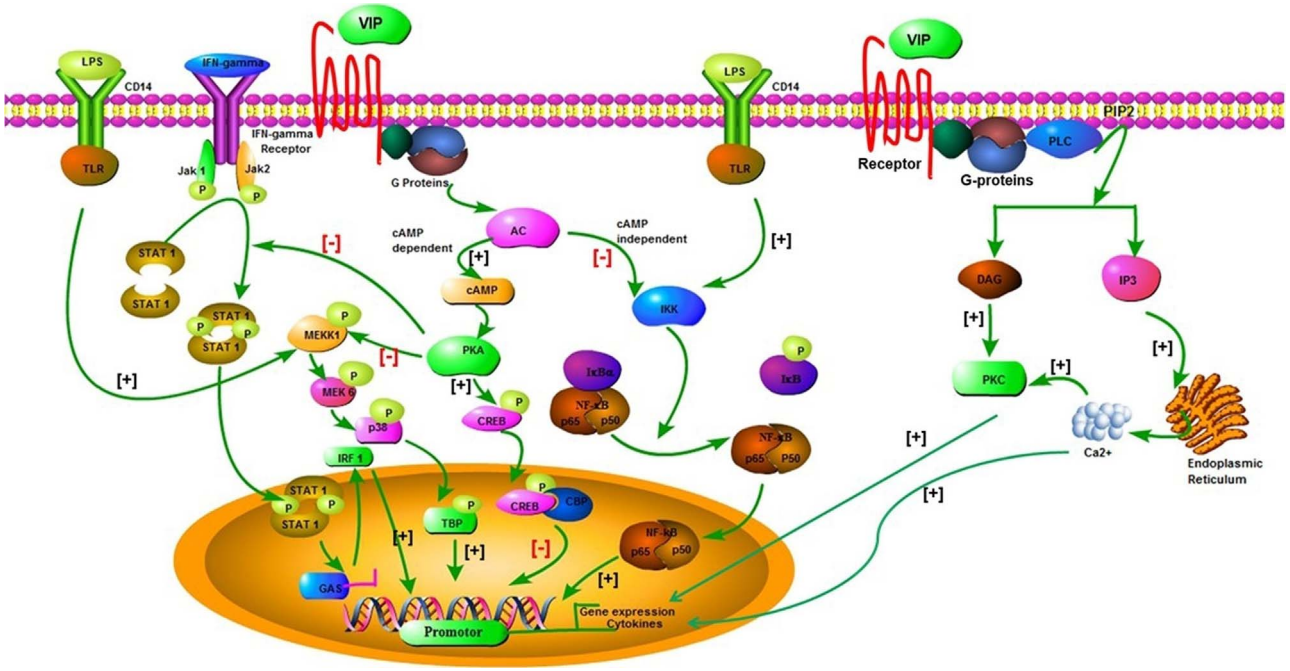

Fig. 1. The summarized mechanistic events operational in VIP mediated signaling pathways. PKA = Protein kinase A; MAP kinase = Mitogen-activated protein kinase; CREB = cAMP response element binding protein; CBP = CRBP binding protein; NF-KB = Nuclear factor KB; TBP = TATA box binding protein; JAK/STAT = Janus kinase/signal transducer and activator of transcription; IκK = inhibitory κB kinase; LPS = Lipopolysaccharides; MEKK1 = MAP/ERK kinase(MEK) KINASE 1; TLR = Toll-like receptor; STAT 1 = Signal transducer and activator of transcription 1; JAK 1 = Janus kinase 1;IRF 1 = Interferon regulatory factor 1; PKC = Protein kinase C; DAG = Diacylglycerol; PIP2: Phosphatidylinositol 4,5-bisphosphate; PLC = Phospholipase C; IP3 = Inositol 1,4,5–triphosphate.

cytokine IL-10 production. VIP has an excitatory effect on monocytes and macrophages but inhibits LPS-induced or IFN-γ-induced inflammatory pathways in these cells. VIP arrest LPS-induced inflammation in monocytes and macrophages via cAMP-dependent or independent mechanisms [54,93]. The presence of VPAC-1 and VPAC-2 receptors on dendritic cells has also been reported [94,95].

4. Mechanistic events involved in VIP mediated signaling

VIP exerts immunomodulatory effects through VPAC-1, VPAC-2, PAC1 and CRTH2 receptors via the stimulation of various protein kinases such as the phospholipase C/PKC and the mitogen-activated protein kinase (MAPK) pathways, as well as the adenylate cyclase/PKA pathway [96]. Further, PAC1 receptor mainly mediates effects via linking with phospholipase C, whereas VPAC-1 and VPAC-2 receptors generally couple to adenylate cyclase. The mechanistic pathways involved in VIP mediated induction of immune responses are depicted in Fig. 1. Two pathways are operational in VPAC mediated response:- cAMP-dependent pathway and cAMP-independent pathway. In cAMP-dependent pathway, the binding of VIP with VPAC receptors increase the intracellular cAMP by stimulating adenylate cyclase that leads to activation of protein kinase A (PKA). The activated PKA further mediates its action via two different mechanisms- through promoting phosphorylation of cAMP response element binding protein (CREB), which finally leads to inhibition of NF-κB. CREB binds to co factor known as CRBP binding protein (CBP), therefore preventing the interaction of CREB with nuclear factor kB (NF-KB). The another downstream effect of PKA activation causes inhibition of phosphorylation of downstream MAP/ERK kinase(MEK) kinase 1 (MEKK1) that leads to inhibitor of MEKK3/6/P38 pathway that subsequently prevents the another NF-κB co factor known as TATA box binding protein (TBP) minimizing the affinity for DNA and inhibit NFkB pathway [54]. In addition, this pathway also blocks the IFN-γ induced inflammatory response by inhibiting phosphorylation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [23].

Apart from above discussed signaling mechanism, there is another cAMP-independent pathway operational in VIP mediated responses that prevent the nuclear entry of NF-κB via inhibiting IκB phosphorylation. The cAMP-independent pathway prevents inhibitory κB kinase (IκK) activity that inhibits the phosphorylation of the IκB and enhances the stabilization of p65/p50/IκB complex. Finally, all these events prevent the nuclear translocation of NFκB subunits. VIP mediated signaling also inhibits the inflammatory response induced by LPS [36,54]. Additionally, the stimulation of other intracellular messenger systems including calcium and phospholipase D have also been reported [24]. Recently, the possible mechanism of association between VIP and CRTH2 receptor has been explored. The study demonstrated that VIP-induced eosinophil chemotaxis in allergic rhinitis patients is mediated through the CRTH2 receptor involving Ca^{2++} independent protein kinase C (PKC) and protein kinase A (PKA) activity. Moreover, VIP-CRTH2 binding involves novel PKC δ, PKCε, PKAα, PKAα IIreg, and PKAɣ cytosol-to-membrane translocation without the change in the total contents of these proteins [18]. Importantly, VIP mediated activation of the particular signal transduction pathway depends on expression of the predominant receptor subtype, cellular level of activation, and use of cell lines [97].

5. Significance of VIP in the allergic diseases

VIP has been proposed to play a key role in many physiological processes occurring in the gastrointestinal tract, airways, cardiovascular system, reproductive system, and endocrine system. The immunomodulatory effect of VIP is indicated by the study in which the peripheral blood mononuclear leukocytes from allergic rhinitis and asthma subjects were incubated with a number of neuropeptides such as VIP, Substance P, morphine, and ACTH and in both normal and allergic subjects, only VIP showed stimulatory effects [98].

5.1. Significance of VIP in asthma pathogenesis

Asthma is a common chronic inflammatory disease of the airways characterized by reversible airflow obstruction, airway hyperreactivity,

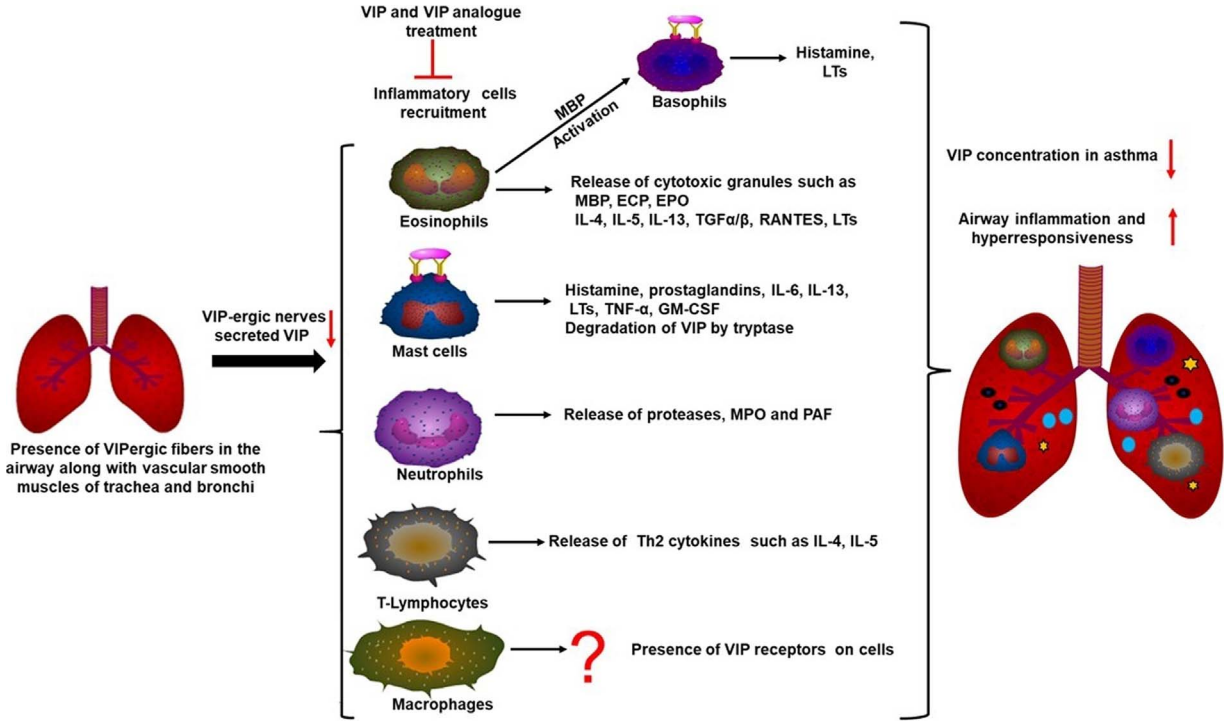
VIP and VIP analogue treatment
Inflammatory cells recruitment
MBP Activation
Basophils
Histamine, LTs
Eosinophils
Release of cytotoxic granules such as MBP, ECP, EPO
IL-4, IL-5, IL-13, TGFα/β, RANTES, LTs
VIP-ergic nerves secreted VIP
Mast cells
Histamine, prostaglandins, IL-6, IL-13, LTs, TNF-α, GM-CSF
Degradation of VIP by tryptase
Presence of VIPergic fibers in the airway along with vascular smooth muscles of trachea and bronchi
Neutrophils
Release of proteases, MPO and PAF
T-Lymphocytes
Release of Th2 cytokines such as IL-4, IL-5
Macrophages
?
Presence of VIP receptors on cells
VIP concentration in asthma
Airway inflammation and hyperresponsiveness

Fig. 2. The significance of VIP in asthma pathogenesis. Decreased VIP level in lungs leads to recruitment of inflammatory cells such as eosinophils, mast cells, neutrophils, lymphocytes in the lungs. These cells release the allergic mediators that promote airway inflammation and hyperresponsiveness. MBP = Major basic protein; ECP = Eosinophil cationic protein; EPO = Eosinophil peroxidase; LTs = Leukotrienes; TNF = Tumor necrosis factor; RANTES = regulated on activation, normal T cell expressed and secreted; TGF = Transforming growth factor; MPO = Myeloperoxidase; PAF = Platelet activating factor; GM-CSF = Granulocyte macrophage-colony stimulating factor.

and mucus hypersecretion. The allergic manifestations involve the release of allergic substances from mast cells, eosinophils, and excessive production of Th2 cytokines such as IL-4, IL-5, IL-13, and IgE antibody [99]. It is estimated that asthma is affecting > 7.0 million children in the United States and the prevalence of the disease is still increasing [100]. A rich supply of VIPergic fibers were observed in the airway along with vascular smooth muscles of trachea and bronchi in the respiratory tract pointing out the role of VIP in the immunopathogenesis of respiratory diseases [101]. As VIP exerts a variety of biological actions, reducing vascular- and bronchial-constriction, and works as a potent anti-inflammatory factor, thus may be used for the treatment of cardiopulmonary disorders such as pulmonary arterial hypertension, asthma and chronic obstructive pulmonary disease (COPD). VIP has the ability to improve blood circulation to lungs and also balancing airway secretions [102]. Furthermore, VIP released from inhibitory non-adrenergic noncholinergic (i-NANC) nerves works as an airway smooth muscle dilator but during allergic condition, VIP mediated effect is attenuated by released inflammatory mediators that may cause airway hyperresponsiveness. The mechanistic role of VIP in asthma pathogenesis is shown by the study in which intraperitoneal administration of VIP eliminated the airway hyperresponsiveness and reduces the inflammation in VIP gene-deficient (-/-) mice [19]. Consistent with this study, VIP gene deficient (-/-) mice showed peribronchiolar airway inflammation along with the production of pro-inflammatory cytokines and airway hyper-responsiveness to inhaled cholinergic agonist methacholine [103]. Further, the significance of VIP was analyzed in VIP gene deficient (-/-) mouse model of sulfite-sensitive asthma in which VIP modulate the oxidant/antioxidant balance in asthma. The wild-type mice with VIP gene have functional lung carbonyl reductase without any symptoms of asthma, whereas VIP-/- mice have abnormal carbonyl reductase and have spontaneous asthma suggesting that deficiency of VIP gene may cause a predisposition to asthma development [104]. The decreased VIP concentration in the bronchoalveolar lavage fluid in rat model is negatively correlated with c-fos protein expression and more prone to asthma attacks [105]. Moreover, the decrease in VIP content in murine lungs, especially in the columnar epithelia of the airways in Aspergillus-treated mice, was also observed [106]. The positive correlation between VIP staining and mast cell infiltration in the smooth muscle layer was also noticed [107]. It is well established that tryptase, a serine proteinase, released after mast cell activation is capable of causing bronchial hyperresponsiveness and recruitment of inflammatory cells in asthma. This effect is probably mediated by activation of other allergic mediators and cleavage of the bronchodilating peptides VIP and peptide histidine-methionine (PHM) [108]. Purified tryptase obtained from human lung extract has the ability to rapidly hydrolyze VIP at multiple sites at Arg12, Arg14, Lys20, and Lys21 and PHM at a single site Lys20 indicating tryptase-mediated degradation of the bronchodilators including VIP may be responsible for bronchial responsiveness in asthma [109]. The effect of VIP administration on neutrophil trafficking in the lungs were also observed demonstrating the systemic or/local administration of VIP analogue decreases cytokine-induced neutrophil recruitment in airways in Sprague-Dawley rats that were treated intratracheally with recombinant interleukin (IL)-1 β [78]. Stimulation of airway smooth muscle (ASM) cell with endogenous mitogens may lead to increased airway resistance/ASM hyperplasia in bronchial asthma. However, VIP has the ability to inhibit ASM cell growth and inhibit the mitogenic effect of histamine by a PKA-mediated mechanism [110]. Further, targeting the VIP receptors can also be promising approach for reducing the asthma severity. Several lines of evidence suggest that there was no correlation exist between severity of asthma and the number of VIP-nerves in the biopsies [111,112]. A study was performed in 25 adult asthmatic patients in which VIP plasma levels were found lower in patients than normal individuals indicating the relevance of VIP in asthma pathogenesis [113]. Collectively, it can be mentioned that VIP acts as an anti-asthma factor as decreased VIP concentration in asthmatic patients leads to increased airway inflammation and hyperresponsiveness. The diagrammatic representation of VIP mediated immune responses in asthma is summarized in Fig. 2.

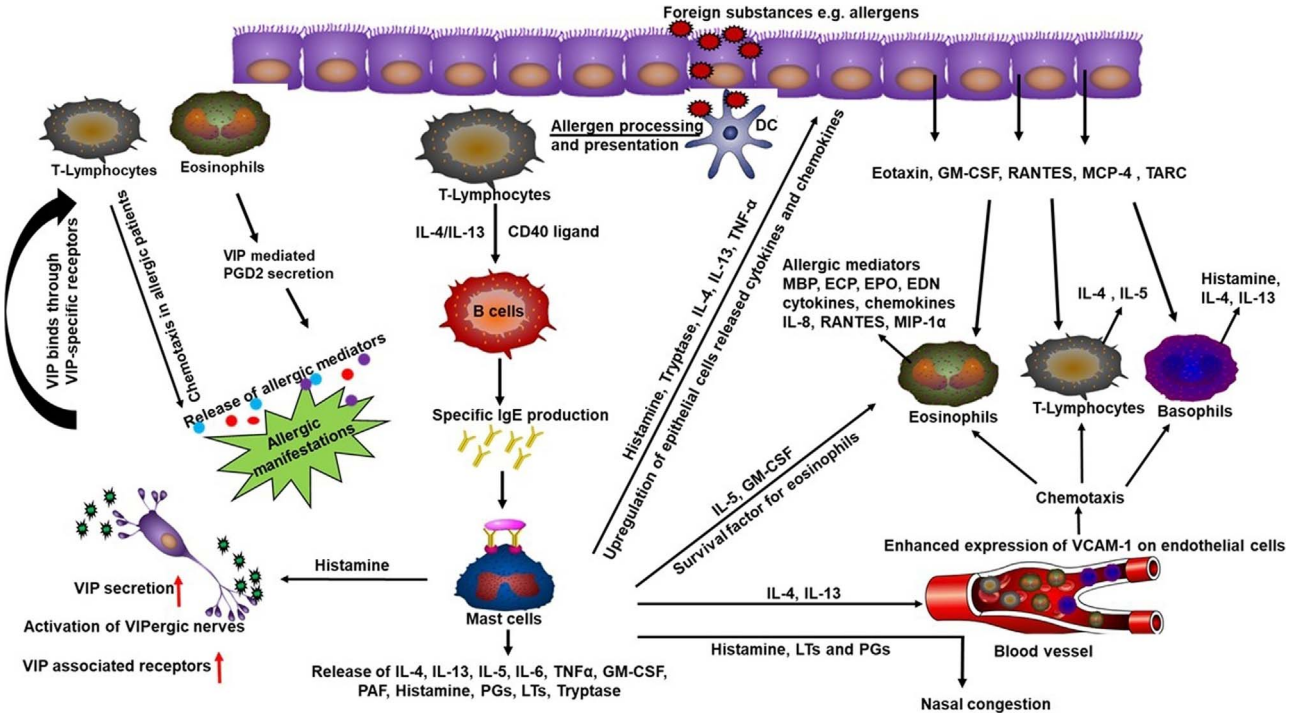

Fig. 3. The significance of VIP in the pathogenesis of allergic rhinitis. Allergic mediators activate VIP-ergic nerves to induce the secretion of VIP which in turn promotes the trafficking of inflammatory cells in the tissue and manifest allergic responses. VCAM-1 = Vascular cell adhesion molecule 1; TARC = Thymus-and activation Regulated chemokine; PGs = Prostaglandins; PGD2 = Prostaglandin D2; DC = Dendritic cells; MCP–4 = Monocyte chemotactic protein-4; EDN = Eosinophil-derived neurotoxin; MIP-1α = Macrophage Inflammatory Proteins −1α.

5.2. Significance of VIP in promoting allergic rhinitis pathogenesis

Allergic rhinitis (AR) is an IgE-mediated immediate allergic reaction with the main symptoms of nasal obstruction, pruritus, nasal itching, sneezing and rhinorrhea [65]. Several allergic mediators such as histamine, leukotrienes, prostaglandins, interleukins, and platelet-activating factor playing role in AR pathogenesis [65]. Nasal biopsy examinations have shown an accumulation of inflammatory cells such as mast cells, eosinophils, and basophils in AR patients [114] and Th2 mediated response is reported [115].

The human nasal mucosa is abundantly innervated by nerve fibers, secretes various neuropeptides that have the impact on the disease pathogenesis. Notably, the enhanced expression of VIP and its receptors (VPAC-1 and VPAC-2) in the nasal mucosa of AR patients were observed suggesting an increased expression level of VIP receptors as one of the possible explanation for nasal hyperresponsiveness in allergic rhinitis patients [116]. Similarly, the significant increase in neuropeptide-containing nerve fibers especially VIPergic fibers were observed emphasized the involvement of innervation in these allergic rhinitis patients [117].

Mucociliary clearance (MCC) is the physical defense mechanism that protects the airway against inhaled pathogens, toxins and allergens [118]. The expression of VIP is observed in the sinonasal epithelium that was found up-regulated in allergic state suggesting the possibility that an increased VIP level in histamine-driven allergic rhinitis may enhance the sinonasal fluid secretion causing allergic rhinorrhea [119]. In the study, allergic rhinitis patients were challenged nasally with histamine or allergen and after histamine challenge, only VIP level was found enhanced in nasal lavages. However, SP, CGRP, and VIP were significantly enhanced immediately after allergen challenge. This data suggest that histamine-induced cholinergic reflexes induce the release of VIP and its crucial role in nasal allergy [120]. Additionally, parasympathetic nerves are involved in the pathophysiology of rhinosinusitis and estimation of secreted VIP in human saliva may be used as markers for parasympathetic nerve activity in these patients. The baseline salivary levels of VIP was significantly elevated between attacks in allergic rhinosinusitis subjects and returned to baseline values following treatment with pseudoephedrine demonstrating that VIP level in saliva may indicate the neuronal mechanisms involved in rhinosinusitis [121].

Posterior nasal neurectomy (cholinergic nerve) has been shown to remarkably improve subjective nasal symptoms in patients with severe allergic rhinitis as it decreases the IL-5 and mast cells in severe AR [122]. Posterior nasal neurectomy (PNN) is a common surgical treatment for allergic rhinitis in Asia and it is based on the concept that posterior nasal neurectomy may induce denervation of the nasal mucosa and relieve the nasal symptoms of allergic rhinitis. The posterior nasal nerve is considered the main source of the sympathetic, parasympathetic and sensory fibers that innervate the nasal mucosa. However, recently rat model of PNN was developed and examined the effects of PNN on allergic rhinitis in ovalbumin-sensitized rats. Although these rats showed reduced nasal secretion, PNN did not affect eosinophils and mast cells infiltration, and other allergic symptoms (i.e. sneezing and nasal scratching). The study points out that PNN may be a therapeutic option for management of hyperrhinorrhea, but not allergic rhinitis hypersensitivity as nerves and secreted neuropeptides regulate only nasal secretion, but not hypersensitivity in AR [123]. Recent literature on allergic rhinitis patients provided the first evidence of the association between VIP and CRTH2 receptor in eosinophil chemotaxis in these patients. The CRTH2 receptor expression by eosinophils in AR patients was found to be up-regulated following VIP treatment. Further, VIP induces PGD2 secretion by eosinophils enhancing the allergic manifestation. This study suggests that VIP-induced eosinophil chemotaxis in AR patients is mediated through CRTH2 receptor [18]. Additionally, tyrosine kinase inhibitors induce the expression of CRTH2 receptor in both human lymphocytes and eosinophils thereby augmenting the VIP/PGD2 induced eosinophils recruitment in allergic rhinitis patients [124]. Taken together, these findings provide preliminary supportive evidence that VIP may be playing a crucial role in AR pathogenesis and there is still need to explore the further

significance of VIP in AR immunopathogenesis. The possible mechanistic aspects and cell types involved in VIP mediated immunological responses in allergic diseases such as allergic rhinitis have been summarized in Fig. 3.

5.3. Significance of VIP in promoting atopic dermatitis pathogenesis

Atopic dermatitis (AD) is a type of skin inflammation and it affects 10%-20% of the population [125,126]. Nervous system modulates the immunologic responses in the skin of AD patients. Altered expression of cutaneous innervation and released neuropeptides in AD patients provoke the immunological responses in the skin by modulating the functions of langerhans cells, keratinocytes, mast cells, and other immune cells [127,128]. Neuropeptides are released by the skin innervating nerves that affect the skin immunity and cell function. Therefore, the better understanding of neuropeptides interaction with skin immune cells/system is necessary for developing new approaches for skin disease treatment. The skin inflammation may be Th1/Th2-mediated and APC cells involved in the Th1 and Th2 process are distinct. Thus, the effect of neuropeptides in cutaneous immunity occurs through a complex mechanism and interaction of neuropeptides with particular immune cells changes the immune response [6]. The existence of VIP- immunoreactive nerve fibers in the deeper part of the dermis close to sweat glands and hair follicles as well as the presence of VIP receptors on keratinocytes in the basal layer of the epidermis have been reported indicating the possible role of VIP in skin physiology [129]. Diminished SP levels and increased VIP levels in lesional skin from AD patients were observed as compared to control skin [130]. VIP concentration is elevated in skin biopsies from patients with eczema, psoriasis and VIP may increase local blood flow in these patients [131].

An increase in the numbers of VIP-positive nerve fibers in lesional psoriatic skin were observed as compared to normal skin [132]. The study by Fisher et al. (2002) demonstrated the marked staining for VPAC-2 mRNA in epidermal cells with most pronounced hybridization signals observed in keratinocytes of the basal layer and in glandular cells surrounded by VIP-immunoreactive nerve fibers. Hair follicle cells next to VIP-positive nerve fibers also showed hybridization signals [133]. The elevated plasma levels of neuropeptides including VIP was reported to be enhanced in AD patients as comparison to normal non-atopic controls [134]. Further, enhanced plasma levels of neuropeptides including VIP was found correlated with the intensity of pruritus in the intrinsic type of AD and the higher risk of IgE-mediated sensitization to moulds in the extrinsic type of AD suggesting neuropeptides may be used as better alternative biomarkers of AD [135]. The enhanced VIP levels were reported in AD patients not only in the skin but also in the serum [20]. Interestingly, computer-induced stress enhanced the allergen-specific skin wheal responses with the concomitant increase in plasma levels of SP and VIP in AD patients aggravating the severity of AD [136]. However, a study performed by Kang et al. (2000) where the action of neuropeptides VIP and SP to affect cytokine release (IFN-gamma & IL-4) in the peripheral blood mononuclear cells (PBMCs) of AD patients were analyzed. The ratios of IFN-gamma: IL-4 production was significantly elevated in the SP treated AD group, although VIP had no specific noticeable modulatory effects on these cytokine production suggesting the no VIP mediated modulatory effects on the cytokine production in AD patients [137]. Only type I VIP receptor (VPAC-1) mRNA was reported to express in normal human keratinocytes while DJM-1 cells (human epidermal keratinocyte cell line) expressed both VPAC-1 and VPAC-2 receptor. VIP also induced the production of inflammatory cytokines (IL-6, IL-8, and RANTES) and these effects were nullified by VPAC-1 selective antagonist indicating that these effects are mediated by type I VIP receptor [138]. It is proposed that in the dermis, inflammatory cells secrete different cytokines which in turn upregulates the expression of VIP receptor thereby enhancing response to nerve fibers released VIP. This nerve endings derived VIP ultimately enhances the proliferation as well as cytokine production by keratinocytes. This cytokine network around keratinocytes may be playing a crucial role in the pathogenesis of inflammatory dermatoses [138]. However, in another study, the role of mast cell in allergic skin disease has been observed. The enhanced VPAC-2 mRNA expression in mast cells was noticed that was increased compared to other receptors such as VPAC-1 or VIP in the human mast cell line HMC-1. Stimulation of HMC-1 cells led to a downregulation of VPAC-2. Similarly, significantly decreased VPAC-2 immunoreactivity in mast cell was noticed in acute atopic dermatitis lesions implicating the role of VPAC-2 receptor in the pathophysiology of atopic dermatitis [58,139]. Taken together, the current pieces of evidence have clearly shown the participation of VIP in the pathophysiologic background of skin inflammatory disorders.

5.4. Significance of VIP in pathogenesis of esophageal disorders

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal disorder that is characterized by heartburn, difficulty in swallowing (dysphagia), and regurgitation of food or sour liquid (acid reflux) [140]. GERD patients who have delayed gastric emptying, have the abnormalities in the peptide-immunoreactive fibers that innervate the gastric external muscle [141]. Interestingly, abnormally high serum VIP level may have a role in GERD pathogenesis. VIP mediated relaxant effect on lower esophageal sphincter causes exposure of esophageal mucosa to harmful acid refluxed that subsequently increases the nitric oxide (NO) levels responsible for low lower esophageal sphincter (LES) pressure [142]. Additionally, the study by Rossiter et al. (1991) demonstrated that the decreased LES resting pressure noticed in patients with Barrett's esophagus and severe gastroesophageal reflux may be due to impairment of the VIPergic innervation that subsequently enhances local release of VIP with possible overflow to peripheral plasma [143]. The symptoms include vomiting, diarrhoea, itching, low blood pressure, and respiratory problems, and sometimes anaphylaxis. In addition, GERD like symptoms is also observed in another esophageal chronic allergic disease termed as EoE. EoE is characterized by esophageal dysfunction, accumulation of $\geq$15 eosinophils/high-powered field, induced mast cell accumulation, basal cell hyperplasia and a lack of response to 8-week proton pump inhibitor treatment. Patients with primary EoE commonly report symptoms that include difficulty in feeding, vomiting, chest pain, dysphagia, and food impaction [144,145]. Most recently, we showed that neuroendocrine cells released VIP in the esophageal mucosa promotes eosinophils and mast cells trafficking and accumulation in all segments of the esophagus, indicating an important role of VIP in the pathogenesis of EoE. Furthermore, we showed that inhibition of VIP-CRTH2 axis ameliorates eosinophils and mast cells inflammation in the esophagus. Therefore, anti-VIP or anti CRTH2 receptor therapy may be beneficial to treat the dysphagia, stricture and motility dysfunction of chronic EoE [63].

VIP have modulatory effects on immune system activity especially on Th1/Th2 balance and may lead to allergic sensitization in children. Notably, VIP showed a positive relationship for allergic sensitization with food allergens [146]. Collectively, it can be clearly mentioned that allergic diseases become the rapidly growing public health problem worldwide and there is still the gap in the understanding of the significance of VIP in other allergic diseases such as Eosinophilic Gastrointestinal Disorders. Therefore exploring the relationship between VIP and allergic diseases may provide the basis for future research to develop therapeutic approaches for the management of these allergic diseases.

6. Therapeutic approaches

Our increasing understanding regarding the impact of VIP in the pathogenesis of allergic diseases proposes the VIP and stable VIP-derived agents as an efficient therapeutical option to cure inflammatory allergic disorders such as asthma, rhinitis, atopic dermatitis, and several eosinophil associated gastrointestinal disorders [22]. The synthesis of

stable peptidase resistant VIP agonist can give promising results to treat bronchial asthma. The recent finding revealed the novel stabilized inhaled VIP agonists for respiratory therapeutics may be used with minimum side effects [147]. The use of VIP may also be a fruitful approach to protect asthmatic patients against histamine-induced bronchoconstriction [148]. Inhalation of VIP analogue Ro 25-1553 (a selective VPAC-2 receptor agonist) leads to a rapid bronchodilatory effect in asthmatic patients without any side effects [149]. Additionally, conjugated alpha-alumina nanoparticle with VIP has been proposed as an effective nano-drug for the treatment of asthma [150]. Additionally, induced expression of VIP and VIP associated receptors were reported in patients with atopic dermatitis [20,129], allergic rhinitis [116] and EoE [63], suggesting the use of stable VIP antagonists or specific VIP receptors antagonist may be the logical approach for improving these inflammatory diseases.

7. Conclusions and future perspectives

VIP is a neuropeptide with a broad distribution in the body that performs pleiotropic functions in several systems and serves as the modulator of immune response. To date, several studies have demonstrated the role of VIP in regulating the recruitment of inflammatory cells in the allergic diseases. Owing to the ability of VIP to activate immune cells of both the innate and adaptive immune system, it may be a decisive neuropeptide in modulating the pathophysiology of allergic diseases. The main concern in the usage of VIP as a therapeutic option is the very short half-life as rapid enzymatic degradation occurs. However, in the light of recent advancement, better stable VIP agonists/antagonists have been developed providing the convincing support to be used as a therapeutic alternative for the treatment of allergic diseases. However, there is still need to conduct more studies to investigate the interaction and cross talk of VIP with the immune cells to get the better idea regarding the pathogenesis of the allergic disease. A better way to see VIP as both anti-inflammatory and pro-inflammatory agent, therefore, the better understanding of VIP immune biology will be helpful to develop efficient future therapeutic strategies to treat allergic diseases.

Conflict of interest

All authors have declared no conflict of interest.

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Dr. Alok K. Verma, PhD, is postdoctoral research fellow at Department of Medicine, Section of Pulmonary Diseases, Tulane University, New Orleans, LA, USA. Dr. Verma's long-term research interest involves to understand the underlying immune mechanism of various cells such as T cells, B cells, mast cells, macrophages and eosinophils in modulating the immune response. Dr. Verma has received his master's degree from University of Lucknow, India and PhD degree in Biological Sciences from the Academy of Scientific and Innovative research (AcSIR), CSIR-IITR, India. He has completed his initial PhD training at CSIR-Indian Institute of Toxicological Research, a Government of India sponsored research organization involved in understanding the mechanism and regulation of toxic agents and their effects on different human organs. His doctoral research work was mainly focused to understand the mechanism involved in the allergenicity of food allergens using in vitro and in vivo model systems. Dr. Verma has identified seven IgE binding proteins which are responsible for chickpea induced allergy in sensitized individuals. He is currently working in the area of eosinophil biology and exploring the role of different involved molecules in the pathogenesis of Eosinophilic esophagitis. Dr Verma is also member of several prestigious scientific societies such as The American Association of Immunologists (AAI), American Gastroenterological Association (AGA), European academy of allergy and clinical immunology (EAACI), and Indian Immunology Society.

Dr. Murli Manohar, PhD, is a post-doctoral research fellow at Tulane University, New Orleans, USA. Dr. Manohar's research interest includes immunological regulation of gastrointestinal disorders such as eosinophilic esophagitis, eosinophilic pancreatitis, fibrosis, and pancreatic malignancy. Currently, he is working on the various the role of eosinophils, IL-5 and IL-18 in the pathophysiology of acute pancreatitis, chronic pancreatitis, eosinophilic pancreatitis, fibrosis as well as pancreatic cancer. Dr. Manohar obtained his Ph.D in Biochemistry from the CSIR-Central Drug Research Institute/ Jamia Hamdrd, INDIA where he studied the pathophysiology and treatment options for endocrine related cancers and explored the anti-tumor effect as well as molecular mechanism of polyphenolic phyto-compound "Epigallocatechin-3-gallate" on endometrial cancer. Dr. Manohar has gained his B.Sc. and M.Sc. form University of Lucknow, India. He serves on the reviewer board of the Cancer Letter, Life Sciences, RBM online, Mediators of Inflammation, and SOJ Journal of Gastroenterology, Pancreatology & Liver Disorders. Dr. Manohar is the member of various scientific societies such as American Association of Cancer Research, American Gastroenterological Association, and American Association of Immunologist.

Dr. Sathisha Upparahalli Venkateshaiah, PhD is Postdoctoral Research Fellow in the Section of Pulmonary Diseases at Tulane School of Medicine, New Orleans, LA. Dr. Sathisha UV had an exceptional background, foundation with his renowned education at University of Mysore, Mysore, India where he graduated with Bachelor of Science. Having excelled in science education, he then undertook PhD training at University of Mysore, Mysore, India. Dr. Sathisha UV skilled in Cancer Biology and Molecular Biology training from an esteemed Central food Technological Research Institute (CSIR), Mysore, India. Dr. Sathisha UV completed his postdoctoral training at Myeloma Institute for Research and Therapy, Winthrop P. Rockefeller Cancer Institute, UAMS, Little Rock, AR, USA, Tulane School of Medicine, New Orleans, LA. Dr. Sathisha UV most important contribution was role of bone marrow microenvironment in Myeloma tumorigenesis. Dr. Sathisha UV's most important contribution was IL-15′s protective role in the pathogenesis of asthma (SATHISHA U V., et al Journal of Allergy and Clinical Immunology (JACI) 2017, In press).

Dr. Anil Mishra, PhD is Edward G. Schlieder Educational Foundation Endowed Chair and Professor of Medicine. He is also the Director of Tulane Eosinophilic Disorder Center in the Section of Pulmonary Diseases at Tulane University School of Medicine. Dr. Mishra's research established that eosinophils are the resident cells of the gastrointestinal tract that home prenatally (Mishra et al., J. Clin. Invest. 1999). He showed that eosinophil active chemokine eotaxin-1 constitutively expressed and has significant role for eosinophils homing into the gastrointestinal tract. He developed the first murine model of eosinophilic esophagitis (EoE) (Mishra et al., J. Clin. Invest. 2001). His findings implicated aeroallergen in the etiology of EoE and suggested that esophageal eosinophilic inflammation is mechanistically regulated by IL-5, IL-13 and eotaxin (J. Immunology 2002, and Gastroenterology, 2003). Furthermore, we also indicated that T cell subset iNKT cells are critical and the source of eosinophil active cytokines in human EoE, and targeting the cell surface receptors of iNKT cells improve EoE in experimental model of EoE (Clinical and Translational Immunology, 2014). Most recently, the laboratory of Dr. Mishra has reported that rIL-15 is a therapeutic molecule for the allergen-induced airway hyperactivity and fibrosis for chronic asthma and other pulmonary functional impairment (J. Allergy Clin. Immunol. 2017). Dr. Mishra is an elected fellow of the American Academy of Allergy Asthma Immunology (FAAAAI) and the American Gastrointestinal Association (FAGA). He has published over 85 articles, book chapters and reviews on molecular mechanisms of pulmonary and gastrointestinal allergic responses in high impact factor journals. Dr. Mishra' research is supported by The National Institutes of Health via NIDDK and NIAID institutes Dr Mishra is also a member of several NIH study sections and serving Editor and Editorial Board member in a number of international journals.